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Identifying early markers of 'late onset' attention deficit and hyperactivity/impulsivity symptoms

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Abbreviated title: Late onset ADHD

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Conclusions: The late versus early onset distinction may align with the distinction between deficits in 'bottom up' versus 'top down' processes previously discussed in relation to ADHD. Results also raise the possibility that later onset symptoms could be predicted based on characteristics in childhood.

Key words: ADHD, sensation-seeking, age of onset, growth mixture modelling

General Scientific Summary

We sought to understand why people first start to experience ADHD symptoms at different stages of their lives. We found that people who were higher in sensation-seeking as 7-year olds were more likely to first show symptoms at later stages. This suggests that age of onset differences could map on to previously hypothesised subtypes of ADHD: ADHD due to impairments in ‘top down’ versus ‘bottom up’ processes.

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Identifying early markers of 'late onset' attention deficit and hyperactivity/impulsivity symptoms

Attention deficit hyperactivity disorder (ADHD) is characterised by pervasive and impairing levels of attentional problems, hyperactivity and impulsivity (American Psychiatric Association [APA], 2013). Traditionally conceptualised as a childhood disorder, there is increasing recognition that, in some cases, onset of clinically significant symptoms may not occur until adolescence, or even adulthood (e.g. Faraone, Kunwar, Adamson, & Biederman, 2009; Moffitt et al., 2015). In response to the evidence that symptoms frequently first appear after the originally defined maximum age of onset criterion of 7, the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; APA, 2013) extended the maximum age of onset to age 12 (APA, 2013; Lin, Yang & Gau, 2016). A major part of the impetus for this was that, when evaluated in adulthood, individuals who met diagnostic criteria for ADHD, except for that pertaining to age of onset (based on retrospective recall), showed remarkably similar profiles of impairment to those meeting criteria with an age of onset before age 7. Research suggested that those with late onset symptoms (after age 7) versus early onset symptoms (before age 7) did not differ substantially in neuropsychological test scores, familial transmission, substance use, co-morbidity patterns, personality traits, quality of life (e.g. Faraone et al., 2009; Faraone, Biederman, Doyle et al., 2006; Faraone, Biederman, Spencer et al., 2006; Lin et al., 2016), or response to stimulant medication (Reinhardt et al., 2007). Though there was some initial evidence that those with late onset symptoms had a greater intellectual impairment than those with early onset symptoms (Faraone, Biederman, Doyle et al., 2006), this observation was not replicated in a later study (Guimaraes-da-Silva et al., 2012). A small number of characteristics were identified that potentially differentiated individuals with early versus late onset symptoms; for example,

some studies suggested that individuals with early onset symptoms scored higher on novelty seeking, were less likely to have a co-occurring anxiety disorder, and showed more hyperactivity/impulsivity than those with late onset symptoms (e.g. Guimaraes-da-Silva et al., 2012; Karam et al., 2009; Lin et al., 2016). However, it is not clear that these factors do not simply reflect a difference in age of identification, rather than onset, as they essentially describe a more 'externalising' profile that would make difficulties easier to recognise (cf. Lin et al., 2016).

A small number of longitudinal studies following individuals in community populations from childhood into adulthood have been conducted (for overviews, see Castellanos, 2015; Faraone & Biederman, 2016). One of the most striking results from these studies – and one that underlines the importance of also studying symptom onset within longitudinal community sample designs – was the small proportion of adults who met diagnostic criteria for ADHD in adulthood (excluding the criterion of onset before age 12) who previously met ADHD diagnostic criteria in childhood. Moffitt et al. (2015) found that most adults (87%) who met diagnostic criteria for ADHD at age 38 had not met diagnostic criteria for ADHD at ages 11, 13, or 15; Caye et al. (2016) found that only 13% of those who met diagnostic criteria at age 18/19 had done so at age 11; and Agnew-Blais et al. (2016) found that only a third of those who met diagnostic criteria at age 18 had done so at ages 5, 7, 10, or 12.

Although those with adult and childhood ADHD were similar in many ways, some potentially important differences were observed. Moffitt et al. (2015) found that, compared with controls who had never met ADHD diagnostic criteria, those who met diagnostic criteria for ADHD in childhood were more likely to be male, to have a diagnosis of anxiety and/or depression, poorer brain integrity, lower WISC IQ (as measured in childhood), a diagnosis of PTSD or have attempted suicide, lower WAIS-IV IQ (as measured in adulthood), and a higher polygenic risk score for ADHD compared with controls. Those who met ADHD

criteria as an adult, however, did not differ significantly from controls on any of these variables. The adults with ADHD were, however, more likely to have a persistent diagnosis of substance dependence, whereas individuals with childhood ADHD did not differ from controls on this measure.

On the basis of the minimal overlap between the childhood ADHD and adult ADHD groups, and apparent differences in neuropsychological, genetic, and psychiatric profiles of the groups, the authors of these studies speculated that childhood and adult ADHD onset may be qualitatively different phenomena, with distinct etiology. However, Agnew-Blais et al. (2016) also noted that individuals with later onset symptoms may have the same underlying liability as individuals with earlier onset symptoms, but with symptoms not manifesting until later in life because difficulties are at first compensated for, or masked by, protective factors, such as high cognitive ability or supportive family environments. In this view, individuals with later onset symptoms do not manifest clinically significant problems until the demands of life increase or until they can no longer rely on compensatory supportive environments to the same extent. In support of this idea, Faraone and Biederman (2016) pointed to the fact that across the above-described longitudinal studies, those with later onset showed some early signs of difficulties associated with ADHD, or commonly co-morbid disorders, even if the symptoms were not severe enough to merit a clinical diagnosis at that stage.

This latter observation highlights one of the limitations of studying ADHD symptoms in a categorical manner; i.e. classifying individuals as exceeding diagnostic thresholds or not; as affected or healthy. Much evidence suggests that ADHD symptoms are continuously distributed in the population at the phenotypic and etiological level (e.g. Groen-Blokhuis et al., 2014). By implication, understanding differences among individuals who show later versus earlier onset ADHD can benefit from examining changes in dimensional measures of symptoms across development. Such an approach can provide a more nuanced, and arguably

more accurate, picture of how symptoms develop within and across individuals. Similarly, if, as some authors have argued, later versus earlier onset symptoms represent expected variation in age of onset of the same disorder due to its multi-factorial etiology, then divisions based on age of onset do not create boundaries demarcating qualitatively distinct disorders, but draw potentially arbitrary lines on a continuous distribution (e.g. Faraone & Biederman, 2016).

To allow for the possibilities of continuous symptom and age of onset distributions, it is important to examine continuous changes in symptom levels across development, rather than categorising individuals as ADHD versus non-ADHD and late onset ADHD versus early onset ADHD. Rather than a priori assuming a meaningful distinction between late and early onset ADHD, methodologies such as growth mixture modelling can be employed to evaluate whether there is empirical support for identifying a potentially meaningful subgroup of individuals who show initially low, but increasing symptom levels over development. These individuals would likely be captured in the above-discussed studies as showing late or adult onset ADHD, but could be more comprehensively described in terms of changes in continuously measured symptoms levels over the course of development.

Several previous studies have used growth mixture modelling to assess whether meaningful subgroups of ADHD symptom trajectories can be identified in both clinical and community samples. This approach differs from the above-discussed studies in that it defines data-driven ADHD symptom trajectory groups based on repeated measurements of symptoms over a given period of development. In these studies, the 'late onset' category of the above-discussed studies would very likely correspond to a class of individuals who had symptom trajectories that begin with low levels in childhood but who show increases over development. The evidence for such a class is mixed (e.g. Arnold et al., 2014; Döpfner et al., 2015; Pingault et al., 2011; Robbers et al., 2011; van Lier, van der Ende, Koot, & Verhulst,

2007). For example, van Lier et al. (2007) and Döpfner et al. (2015) identified no group with initially low but increasing symptoms over time. These studies utilised community samples and spanned ages 4-18 and 7-19 respectively.

Similarly, Arnold et al. (2014) measured ADHD symptoms across ages 6-12 in a clinical sample and identified an initially low but increasing symptom group for hyperactivity/impulsivity only.

If an 'initially low but increasing ADHD symptom' group is identifiable, whether these individuals can be differentiated from individuals who begin with, and remain, low on ADHD symptomology is an important question with regards to whether later problems related to ADHD can be predicted based on early markers. Identifying early markers of being at risk of showing symptom increases can facilitate more timely identification when problems become clinically significant and can indicate which individuals may benefit most from preventive interventions. Another key question is whether individuals with initially low but developmentally increasing symptoms differ from those with persistently high levels of ADHD symptoms from childhood. Answers to this question can provide valuable information about whether individuals who first experience difficulties at different developmental stages differ in important ways, and thus represent potentially clinically meaningful subtypes. In this study, we sought to answer these questions using eight waves of ADHD symptom data from a normative sample measured from ages 7 to 15. Our primary objectives were to: 1) evaluate whether a meaningful 'initially low but increasing' ADHD symptom subgroup could be identified; 2) identify baseline factors that differentiate this group from those with persistently high or persistently low ADHD symptoms.

As there is limited prior evidence upon which to base hypotheses about childhood variables that could predict whether a child who exhibits little ADHD symptomology at age 7 or 8 would show increases in symptomology, we began by focussing on traits, behaviours and

mental health symptoms with a hypothesised association with ADHD symptoms. The basic premise was that, even if ADHD symptoms themselves are yet to manifest, associated traits and behaviours could, nonetheless, be present or beginning to emerge.

First, we evaluated whether gender predicts ADHD symptom trajectories. ADHD is considerably more prevalent in boys than in girls, with a sex ratio of around 3:1, and manifests differently in both primary symptoms and patterns of co-morbidity (e.g. Gershon & Gershon, 2002). However, there is some evidence that among those who develop ADHD symptoms, females may do so later than males, resulting in an adulthood ADHD sex ratio closer to 1:1 (e.g. Agnew-Blais et al., 2015; Moffitt et al., 2015).

Second, we evaluated whether the personality characteristics of sensation seeking (measured at age 7) and risk taking (measured at age 8) predicted symptom trajectories. There is evidence that these psychological traits and their putatively underlying neurocognitive traits are elevated in clinical ADHD and correlated with ADHD symptoms in the general population (e.g. Graziano et al., 2014; Hines & Shaw, 1993; Humphreys & Lee, 2011; Rooney, Chronis-Tuscano, & Yoon, 2011).

Third, we evaluated whether the common behavioural correlate of ADHD - reactive aggression - predicts symptom trajectories. Reactive aggression can be defined as 'emotionally hot' aggressive behaviour, representing a response to perceived threat or provocation (e.g. Raine et al., 2006). Reactive aggression and ADHD have been proposed to have common roots in deficits in the neurocognitive processes mediating emotion regulation; specifically, in the ability to inhibit negative emotional reactions to stimuli and to effectively regulate resulting emotional states (e.g. Murray, Obsuth, Zirk-Sadowski, Ribeaud, & Eisner, 2016; Saylor & Amann, 2016).

Finally, we evaluated whether anxiety, a common psychiatric co-morbidity of ADHD, predicts symptom trajectories. Anxiety is prevalent in ADHD, occurring in approximately

15-35% of children with ADHD, as compared to only 5-15% of the general population (e.g. see Schatz & Rostain, 2006). While the primary reasons for the association (and by implication the temporal ordering of ADHD and anxiety onset) remains to be fully resolved, the association can already be observed in pre-schoolers (Overgaard, Aase, Torgersen, & Zeiner, 2016), suggesting a relation that begins relatively early in life. Anxiety, could, therefore possess predictive power with regards to the later onset of ADHD symptoms.

Method

Participants

Participants were from the Zurich project on the social development of children and youths (z-proso); a longitudinal cohort study of child behavioural development with a focus on anti-social and pro-social behaviours. The sample in the current study are the 1571 (761 female, 810 male) for whom ADHD symptom data are available for at least one of the eight measurement waves between ages 7 and 15. They represent 94% of the 1675 target sample. The target sample was defined according to a stratified (by school size and location) random sampling procedure that selected 56 schools. All children entering the first grade in participating schools in 2004 were invited to take part. Data were then collected across eight measurement waves when the participants were of median age 7.45, 8.23, 9.21, 10.70, 11.60, 12.63, 13.88, and 15.68 (henceforth rounded down to the nearest whole number). The numbers of participants contributing data at each of these waves were 1338, 1314, 1287, 1262, 1061, 972, 1239, and 1267, respectively. Active written parental consent was required for the first six years of participation in the study. Parents were offered a financial incentive equivalent to approximately 30 USD. At age 13 and beyond, the participants themselves were required to give their active consent, while parents received an information letter that allowed them to opt out their child. Participants were offered a financial incentive worth approximately 30 USD for their participation at age 13 and 50 USD at age 15. Given the

minimally intrusive nature of the study design, questions, and intervention, ethical approval was not required according to the Swiss regulations (where the study was conducted). Informed consent from the parents and/or youths were obtained in accordance with the relevant national regulations and all data were processed and stored according to data protection regulations.

Measures

ADHD, anxiety, and reactive aggression. ADHD, anxiety, and reactive aggression symptoms were measured using the relevant subscales of the Social Behavior Questionnaire (SBQ; Tremblay et al., 1991). Four items refer to attention deficit symptoms and four items refer to hyperactivity/impulsivity symptoms; three items refer to anxiety; and three items refer to reactive aggression. Item contents in English are provided in Supplementary Materials. Item responses were provided on a five point Likert scale from *never* to *very often*. The reliability and validity of the SBQ has been supported in previous research, including in the current sample (e.g. Murray, Eisner, & Ribeaud, 2016; Tremblay et al., 1991).

The SBQ was administered to the children's teachers in German and in paper and pencil format. For the majority of children, the same teacher taught and provided ratings for them between grades one and three; i.e. at ages 7, 8, and 9. They then had another teacher between grades four to six; i.e. at ages 10, 11, and 12. At ages 13 and 15, the participants were in secondary school. During the first three waves of data collection, teachers were not compensated for their participation, but after this, those with at least seven participants in their class received a book voucher worth approximately 50 USD. The numbers of teachers providing ratings at the measurement waves included in this study were: 113, 148, 217, 274, 265, 258, 366, and 423, respectively. z-proso also includes parent- and self-reported ADHD questionnaire measures; however, the parent-reported measures are only available for the

period spanning ages 7 to 10 and self-reported measures are only available for the period spanning ages 13 to 17. As such, only teacher-reported data- that spans both childhood and adolescence- were included in the current study.

Sensation seeking. Sensation seeking was measured at age 7 using an adapted version of the travel game developed by Alsaker and Gutzwiller-Helfenfinger (2010). Individual assessments were carried out by specially trained investigators during regular school lessons. The children are invited to play a board game in which they move between 'stations'. At each station they choose between two pretend options. For nine of the stations, one of the options is 'risky/thrilling', the other of which is 'not risky/thrilling'. For three of the stations, the choice is between an 'immediate gratification' and a 'delayed gratification' option. A sensation seeking score is derived from the responses at the nine risky/thrilling versus not risky/thrilling stations. Example options include: choosing to ride a carousel versus a rollercoaster; watching a funny cartoon versus a scary movie; and riding a fire-spitting dragon versus a fairy-tale goose. As compared to the original version, the version used in z-proso uses an alternative item ordering, redesigned game board, and includes the three above-mentioned stations measuring immediate/delayed gratification. In this study, we focussed only on the sensation seeking items, deriving a sensation seeking trait estimate from the nine relevant stations.

Risk taking. Risk taking was measured at age 8 using an abbreviated version of the balloon analogue risk task (BART; Lejuez et al., 2002). Individual assessments were carried out by specially trained investigators during regular school lessons. The BART is a computerised behavioural assessment of risk taking. The task involves the children playing a game in which they earn points by inflating a balloon by clicking a 'pump' button. The more the balloon is inflated, the more points are earned; however, at some point the balloon is programmed to burst, resulting in all points from that round being lost. Children played a

total of 20 rounds. Several scoring methods have been suggested; for this study we used the number of balloons burst over the 20 rounds, as this was judged to provide the closest conceptual similarity to the risk taking behaviours observed in ADHD.

Statistical Procedure

We began by obtaining factor scores from latent variable models of all phenotypes, except the risk taking scores which were simply the raw observed BART scores derived directly from the observed scores on the individual trials. ADHD was specified as a longitudinal first-order oblique factor model with attention deficit and hyperactivity/impulsivity as correlated factors. Scaling and identification were achieved by fixing the mean and variance of the attention deficit and hyperactivity/impulsivity factors at age 7 to 0 and 1 respectively, and the intercept and loading of the first item of each first-order factor equal across time. Residual covariances between the same items at different waves were freely estimated. Anxiety, reactive aggression, and sensation seeking were all treated as single latent variables with latent factor mean=0 and variance=1 scaling and identification constraints. All models were estimated using maximum likelihood estimation, except that for sensation seeking which, due to its dichotomous response format, was estimated using weighted least squares means and variances (WLSMV) estimation. All models were estimated in *Mplus 7.31* (Muthén & Muthén, 2014). Factor score determinacies were all >0.90 for ADHD, anxiety, and reactive aggression. They were not computable for sensation seeking due to the estimation method used.

We began by fitting growth mixture models with varying numbers of latent trajectory classes to the attention deficit and hyperactivity/impulsivity factor scores estimated as described in the previous section. To take account of the fact that the majority of youth were rated by the same teacher across the first three waves and the last three waves (with a teacher change in between), we included residual covariances between attention deficit (or

hyperactivity/impulsivity) factor scores across waves 1 to 3 on the one hand and across waves 4 to 6 on the other. Model fit was substantially improved by including these residual covariances and the majority of them were statistically significant. This supports the idea that excess covariation due to the same rater source is important and that reliance on a single rater across time would tend to result in an overstatement of the continuity of ADHD symptoms over development. However, the disadvantage of having a change in rater over time is that changes in symptom could partly reflect changes in rater characteristics. If these effects are marked, they could, for example, lead to an inflection point at the rater change and potentially, in turn, to the detection of spurious classes. We thus examined plots of the mean factor scores for the attention deficit and hyperactivity/impulsivity phenotypes across time to check for evidence of qualitative group-level changes in symptoms that coincided with the teacher change; however, no such changes were detected.

We considered models including linear and quadratic growth only, as preliminary analyses suggested estimation problems consistent with over-parameterisation when including higher-order growth terms. To choose the best model, we relied primarily on the Lo-Mendall-Rubin (LMR) likelihood ratio test and the Vuong-Lo-Mendell-Rubin (VLMR) likelihood ration test.

The *p*-value for these tests assess whether a model with k-1 classes should be rejected in favour of a model with k classes. We also considered information theoretic criteria, giving the highest weight to Bayesian information criterion (BIC). Models with lower (more negative) Akaike information criterion (AIC), BIC and sample size adjusted BIC (saBIC) values are considered better fitting. We considered models with up to six latent classes only, to avoid over-parameterisation and the inclusion of classes too small to provide adequate power to test our category membership prediction hypotheses.

To predict membership in the trajectory classes identified in the first step, we used what has been termed the 'three step approach' by Asparouhov and Muthén (2014). In this method, a most likely class membership variable is created using the latent class posterior distribution from the latent class models described above. Then, this variable is regressed on the predictors, taking into account misclassification variance in the creation of the most likely class membership variable. Attention deficit and hyperactivity/impulsivity categories were separately regressed on each of our predictors in a series of univariate models. We present both unadjusted results and results adjusted for gender.

Results

Model fit statistics for tested models are provided in Supplementary Materials along with model parameters. Both were considered when choosing the optimal class solution. For the linear Growth Mixture Models (GMMs) for the attention deficit phenotype, AIC, BIC and saBIC all suggested that either the 4-class or the 6-class model was best fitting (both were substantially better fitting than the 5-class model). LMR and VLMR suggested that either a 3-class or 6-class solution was to be preferred. Inspection of the 3 and 6 class solutions; however, suggested that the 3-class solution blurred a potentially important distinction between 'initially low but increasing' and 'low stable' classes. Information theoretic criteria, however, tend to err on the side of class over-extraction (e.g. Nylund et al., 2007) and the 6-class solution contained several classes that were of low prevalence. On balance, the 4-class solution was preferred. For the linear+quadratic growth variants of the attention deficit models, the information theoretic criteria continued to decrease with the addition of further classes; however, after 4 classes estimation problems began to appear. In particular, negative variance estimates were obtained for the quadratic slope factors (or if these were fixed to small positive values, other out of range estimates appeared). As these kinds of issues can be symptoms of over-parameterisation, we did not consider quadratic growth for the attention

deficit models with more than 4 classes further. In terms of the 1-4 class solutions, LMR and VLMR both suggested that the 4-class solution should be preferred. Comparing a 4-class solution with linear growth to a 4-class solution with both linear and quadratic growth, the latter was better fitting based on information theoretic criteria. However, examining model parameters, the quadratic growth factor mean was significant only for one class and only marginally so. The quadratic growth factor also covaried strongly with the linear growth factor. Together, these observations suggested that the model with both linear and quadratic growth was likely over-parameterised. Overall we, therefore, preferred the 4-class solution with only linear growth as our preferred growth mixture model for the attention deficit phenotype.

For the linear GMMs for the hyperactivity/impulsivity phenotype, LMR and VLMR suggested that a five-class solution should be preferred while the information the information theoretic criteria suggested that a 6-class solution was best fitting. We also considered the 4-class solution because the *p*-values associated with LMR and VLMR were close to .05. Examining the model parameters for these three solutions, the 4-class solution was preferred on balance because the 5- and 6- class solutions contained several low prevalence classes.

For the linear + quadratic variant of the GMMs for the hyperactivity/impulsivity phenotype, estimation problems as described for the attention deficit phenotypes arose at the 4-class solution and beyond. Considering all evidence together, on balance a 4-class linear growth model was judged optimal for this phenotype.

Key parameters for the models judged as optimal based on LMR, BIC, and an examination of model solutions are provided in Tables 1 and 2. The trajectory classes for both phenotypes could be characterised as 'high stable', 'high decreasing', 'low increasing', and 'low stable'. The trajectories are plotted in Figures 1 and 2. In both cases, the biggest class was the low stable class. By the end of the studied period, the low increasing class had

similar expected symptom levels to the high stable class. The cross-tabulation of category membership for attention deficit and hyperactivity/impulsivity trajectories is provided in Table 3. Category membership across the phenotypes was significantly associated [χ^2 (9) = 1101.5, p<0.001].

Results of the multinomial regression predicting class membership from age 7 characteristics are provided in Tables 4 and 5. Results are provided in two parameterisations; where the reference group is the low stable and where the reference group is the high stable group. Only gender and sensation seeking significantly predicted being in the late onset attention deficit group, as compared to the low stable group. Relative to the high stable category, lower anxiety, lower reactive aggression, and lower risk taking significantly increased the chances of being in the late onset category.

When considering hyperactivity/impulsivity category membership, (male) gender and (higher) sensation seeking were again the only significant predictors of being in the late onset category, relative to the low stable category. Sensation seeking was, however, no longer significant after controlling for gender. When the reference category was the high stable trajectory group, lower sensation seeking, lower anxiety, and lower reactive aggression all significantly predicted membership in the late onset group; however, sensation seeking was again not significant after controlling for gender.

Discussion

In the current study, we evaluated whether a meaningful subgroup corresponding to late onset individuals could be identified in a normative sample of youth measured in eight waves between the ages of 7 and 15. We tested whether these individuals could be distinguished from those who never go on to develop high levels of ADHD symptoms, based on candidate early markers.

We identified four subtypes of symptom trajectory for both attention deficit and hyperactivity/impulsivity symptoms. These could be characterised as low stable, high stable, high decreasing, and low increasing, where low/high refers to baseline symptom levels and stable/decreasing/increasing refers to the slope of symptoms across ages 7 to 15. Mapping these onto the groups typically found in studies of the development of clinical ADHD status, these groups would correspond to 'unaffected', 'early onset/persistent', 'remitting', and 'late onset', respectively. In line with past research, the majority of the sample was in the low stable trajectory group (63% for attention deficit and 73% for hyperactivity/impulsivity), with between 5% and 20% of participants assigned to a trajectory class showing expected high levels of ADHD symptoms at some point across the course of development.

We assessed predictors of membership in the late onset category relative to two different reference categories. To determine if there are any early markers of later onset ADHD symptoms in children initially showing only low symptom levels, we compared late onset to the unaffected group. To evaluate the baseline similarity between those with earlier versus later onset of symptoms, we compared the late onset group to the early onset/persistent group to assess whether patterns of risk factors differed between these groups. Being male and higher in sensation seeking predicted being in the late onset, compared with unaffected, group for both attention deficit and hyperactivity/impulsivity, although the sensation seeking effect was attenuated to non-significance controlling for gender in the case of the latter.

The observation that higher sensation seeking predicted increases in symptoms among those who initially showed only low levels raises the possibility that this trait is an early marker of future problems. It may also a hint at partly distinct etiologies for earlier and later onset symptoms. In particular, previous authors have made a distinction between ADHD symptoms due to deficits in 'top down' versus 'bottom up' processes (e.g. Graziano et al., 2014). Here, top down processes refer to those that are pre-frontally mediated, require

effortful control, and are tapped by performance on traditional executive functioning tasks. Bottom up processes refer to putatively sub-cortically mediated reactive responses to immediate incentives and stimuli, manifesting in traits such as emotional reactivity and sensation seeking (e.g. Blaskey, Harris, & Nigg, 2008; Graziano et al., 2014; Martel, Von Eye, & Nigg, 2010; Sonuga-Barke, 2003). One possibility is that those with symptoms relating to deficits primarily in bottom up processes do not manifest symptoms until later in development, perhaps as environmental stimuli come increasingly under the control of the youth themselves. Another possibility is that sensation-seeking traits predispose individuals to engage in high risk behaviour that could lead to subtle damage to vulnerable parts of the brain during development, increasing the likelihood of ADHD symptom increases beyond childhood. Murray et al. (2017), for example, noted that high levels of substance use in adolescence could adversely affect still-maturing prefrontal regions leading to behaviour regulation deficits associated with ADHD. However, they found no evidence that higher levels of substance use (tobacco, cannabis, alcohol) in adolescence were related to later increases in ADHD symptoms. Other high risk behaviours such as hard drug use or behaviours leading to accident and injury remain to be investigated. The fact that sensation seeking was overall (slightly) more strongly associated with hyperactivity/impulsivity class membership is also consistent with the hypothesis that attention deficit symptoms versus hyperactivity/impulsivity symptoms map on to top down and bottom up processes, respectively (Martel et al., 2010).

Anxiety, reactive aggression, and risk taking did not predict membership in the late onset class, relative to the unaffected class, suggesting that they do not provide early indications of later ADHD symptoms. Lower levels of these traits did, however, significantly predict membership in the initially low but increasing class, relative to the early onset/persistent class. The causal pathways linking ADHD symptoms with these variables

are not yet fully mapped out and the lack of predictive information about later ADHD symptoms would be consistent with the idea that they primarily reflect outcomes of ADHD symptoms.

Limitations

Finally, it is important to consider the limitations of the current research. First, we relied on only a single rater (teachers); however, it is common for different raters to provide unique and/or conflicting information about phenotypes such as ADHD (e.g. De Los Reyes, 2011). Second, our measure of ADHD symptoms was administered in the context of a large cohort study and was thus brief and general. Replicating the current results using a comprehensive and well-validated measure such as the Swanson, Nolan and Pelham rating scale (SNAP-IV) or Strengths and Weaknesses of ADHD symptoms and Normal Behaviour (SWAN; Swanson et al., 2012) will be and important extension to the current study. In addition, although our sample size was relatively large at > 1500, larger samples would provide greater scope to investigate the predictors of membership in lower prevalence classes, such as those identified in the 5 and 6 class solutions in the current study. Similarly, larger samples and more time points would potentially afford greater scope to investigate classes with non-linear growth. Finally, fit statistics for model selection are not definitive guides to choosing optimal class number growth mixture solutions and this decision is necessarily subjective. As such, we provide all latent class fits and solutions considered in the current study in order that other researchers may make their own determinations as to the optimal class solutions in the current dataset.

Conclusion

A substantial minority of youth show ADHD symptom trajectories that begin low and increase over the course of development. Membership in this subgroup is predicted by sensation seeking levels at age 7. This suggests a candidate early marker for late onset

ADHD and possible differences in etiology between late and early onset ADHD corresponding to the previously outlined distinction between ADHD symptoms due to deficits in top down versus bottom up processes.

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Denis Ribeaud studied sociology and social psychology at the University of Zurich and obtained a PhD in criminology from the Criminological Institute of the University of Lausanne. Since 2003 he has been working as the scientific coordinator of the Zurich Project on the Social Development of Children and Youths (z-proso), which he has been co-directing since 2011. He has also directed the last two surveys on youth violence in the canton of Zurich, which provide information on the long-term development of youth violence.

Table 1: Model parameters for attention deficit symptoms 4 class model

Class	Proportion (N)*	Intercept (SE)	Linear Slope (SE)
1 - High stable	0.20 (311.13)	0.82 (0.09)	0.07 (0.14)
2 - High decreasing	0.10 (151.01)	1.19 (0.09)	-1.49 (0.15)
3 - Low stable	0.63 (996.49)	-0.48 (0.03)	-0.05 (0.04)
4 - Low increasing	0.07 (112.36)	-0.60 (0.15)	1.65 (0.16)

***** Based on posterior probabilities. Entropy = 0.74

Table 2: Model parameters for hyperactivity/impulsivity 4 class model

Class	Proportion (N)*	Intercept (SE)	Linear Slope (SE)
1 - High stable	0.08 (125.27)	1.10 (0.23)	0.23 (0.23)
2 - High decreasing	0.13 (215.37)	1.33 (0.10)	-1.69 (0.14)
3 - Low stable	0.73 (1144.22)	-0.41 (0.02)	-0.29 (0.03)
4 - Low increasing	0.05 (86.04)	-0.53 (0.22)	1.74 (0.34)

***** Based on posterior probabilities. Entropy = 0.871

Table 3: Cross-tabulation of attention deficit and hyperactivity/impulsivity category membership

		Hyperactivity/impulsivity category			
		High stable	**High decreasing**	**Low stable**	**Low increasing**
Attention deficit category	**High stable**	108	87	102	18
	High decreasing	2	69	60	0
	Low stable	9	44	966	20
	Low increasing	8	1	37	40

Table 4: Univariate multinomial regression parameters predicting late onset attention deficit symptom trajectory category membership

	Reference category = low stable				Reference category = high stable			
Predictor	**OR**	***p***	**Adjusted OR***	***p***	**OR**	***p***	**Adjusted OR***	***p***
Gender	0.33	0.001	n/a	n/a	1.65	0.21	n/a	n/a
Sensation seeking	1.89	<0.001	1.45	0.048	0.69	0.07	0.81	0.38
Anxiety	0.66	0.09	0.64	0.07	0.40	0.001	0.40	0.001
Reactive aggression	1.04	0.85	0.99	0.97	0.35	<0.001	0.36	<0.001
Risk taking bursts	1.01	0.85	1.01	0.91	0.87	0.047	0.87	0.04

Note. OR = odds ratio

* Adjusted OR is controlling for gender.

Table 5: Univariate multinomial regression parameters predicting late onset hyperactivity/impulsivity symptom trajectory category membership

	Reference category = low stable				Reference category = high stable			
Predictor	**OR**	***p***	**Adjusted OR***	***p***	**OR**	***p***	**Adjusted OR***	***p***
Gender	0.21	<0.001	n/a	n/a	1.63	0.33	n/a	n/a
Sensation seeking (age 7)	2.06	<0.001	1.35	0.13	0.59	0.03	0.57	0.06
Anxiety (age 7)	0.78	0.16	0.77	0.14	0.61	0.02	0.62	0.03
Reactive aggression (age 7)	1.22	0.21	1.16	0.45	0.37	<0.001	0.36	<0.001
Risk taking bursts (age 8)	1.02	0.71	1.02	0.79	0.87	0.07	0.87	0.07

Note. OR = odds ratio

* Adjusted OR is controlling for gender.

Murray, A. L., Eisner, M., Obsuth, I., & Ribeaud, D. (2017). Identifying Early Markers of “Late Onset” Attention Deficit and Hyperactivity/Impulsivity Symptoms. *Journal of Attention Disorders*, In Press.

Figure 1: Latent trajectories for attention deficit symptoms

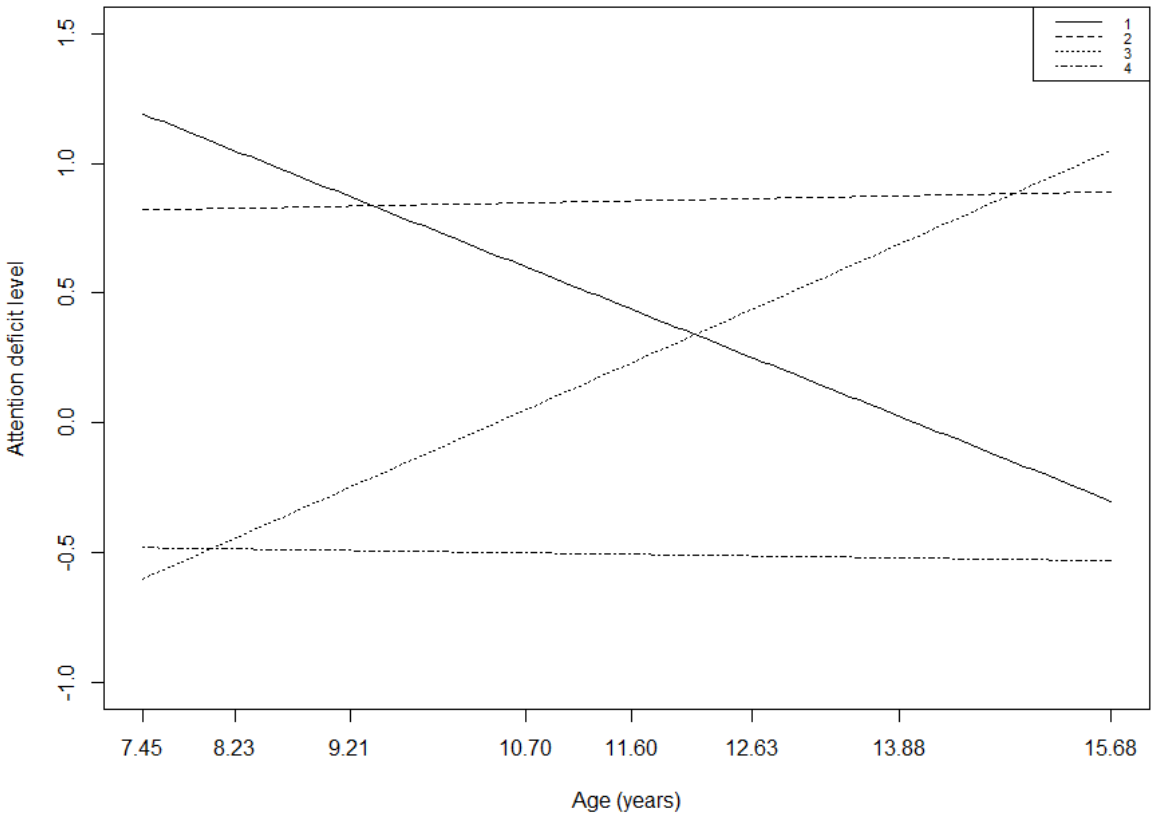
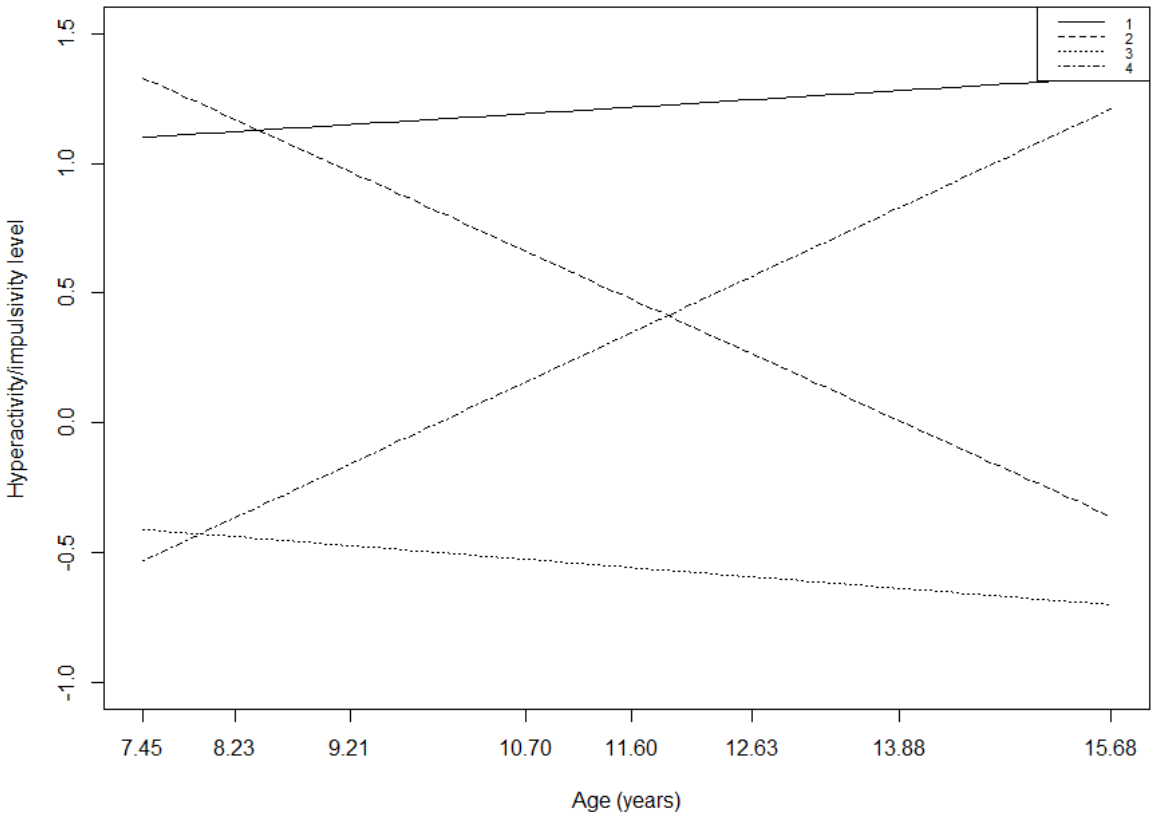


Figure 2: Latent trajectories for hyperactivity/impulsivity symptoms



Supplementary Materials

Table 1:
Attention deficit symptoms hyperactivity/impulsivity symptoms, reactive aggression and anxiety items

SBQ Subscale	Item content in English
	He/She cannot settle to anything for more than a few moments.
Attention deficit	
Attention deficit	He/She is distractible, has trouble sticking to any activity.
Attention deficit	He/she can't concentrate, can't pay attention for long.
Attention deficit	Is inattentive.
Hyperactivity/impulsivity	He/She is impulsive, acts without thinking.
Hyperactivity/impulsivity	He/She hasdifficulty awaiting turn in games or groups.
Hyperactivity/impulsivity	He/She can't sit still, is restless, or hyperactive.
Hyperactivity/impulsivity	Fidgets.
Reactive aggression	He/She reacts in an aggressive manner when teased.
Reactive aggression	He/She reacts in an aggressive manner when contradicted.
Reactive aggression	He/She reacts in an aggressive manner when something is taken from him/her.
Anxiety	He/She cries a lot.
Anxiety	He/She is nervous, highstrung or tense.
Anxiety	He/She is too fearful or anxious.
Anxiety	He/She is worried.

Table 2: Model fits for the growth mixture models for attention deficit

Number of classes	LMR	*P*	VLMR	*p*	AIC	BIC	saBIC
Linear							
1	-	-	-	-	24523.124	24624.954	24564.595
2	158.841	<.001	166.035	<.001	24363.089	24480.997	24411.108
3	58.398	.15	61.043	.14	24308.045	24442.031	24362.612
4	60.492	<.001	63.232	<.001	24250.802	24400.867	24311.918
5	0.002	.002	0.002	.002	24256.806	24422.950	24324.469
6	22.371	.46	23.385	.44	24214.970	24397.192	24289.181
Linear + quadratic							
1	-	-	-	-	24481.971	24605.239	24532.173
2	160.864	.010	166.329	.008	24323.643	24468.348	24382.575
3	49.706	.004	51.394	.003	24280.248	24446.392	4347.912
4	65.896	.153	175.045	.147	24206.673	24394.255	24283.067

Table 3: Model fits for the growth mixture models for hyperactivity/impulsivity

Number of classes	LMR	*p*	VLMR	*p*	AIC	BIC	saBIC
Linear							
1	-	-	-	-	24257.918	24359.748	24299.389
2	443.390	<.001	463.473	<.001	23800.445	23918.354	23848.465
3	184.581	<.001	192.941	<.001	23613.504	23747.491	23668.071
4	130.065	.03	135.956	.028	23492.540	23642.605	23553.655
5	65.714	.64	68.690	.63	23424.769	23590.913	23492.432
6	107.487	.21	112.355	.20	23315.698	23497.920	23389.909
Linear + quadratic							
1	-	-	-	-	24229.140	24352.407	24279.341
2	489.236	.01	505.855	.01	23731.284	23875.990	23790.217
3	262.610	.01	271.531	.01	23533.352	23699.495	23601.015

Table 4: Parameter Estimates for 1-6 class linear growth models for attention deficit

Class	Class prevalence	Intercept Mean	Slope Mean	Intercept-slope covariance
		1-class model		
Class 1	1	-0.07*	-0.04	-0.30*
		2-class model		
Class 1	.71	-0.49*	0.09	-0.18*
Class 2	.29	0.91*	-0.35*	-0.18*
		3-class model		
Class 1	.67	-0.48*	-0.01	-0.16*
Class 2	.19	1.14*	-0.80*	-0.16*
Class 3	.14	0.23	0.88*	-0.16*
		4-class model		
Class 1	.10	1.19*	-1.49*	-0.09*
Class 2	.20	0.82*	0.07	-0.09*
Class 3	.08	-0.60*	1.65*	-0.09*
Class 4	.63	-0.48*	-0.05	-0.09*
		5-class model		
Class 1	.10	1.19*	-1.49*	-0.09*
Class 2	.63	-0.48*	-0.05	-0.09*
Class 3	.20	0.82*	0.07	-0.09*
Class 4	.07	-0.59*	1.65*	-0.09*
Class 5	<.01	-0.48*	-0.05	-0.09*
		6-class model		
Class 1	.06	-0.84*	1.71*	-0.06
Class 2	.08	1.04*	-1.62*	-0.06
Class 3	.21	0.21*	0.05	-0.06
Class 4	.06	0.60*	0.87*	-0.06
Class 5	.09	1.43*	-0.67	-0.06
Class 6	.50	-0.61*	-0.07	-0.06

Note. *statistically significant (p<.05).

Table 5: Parameter Estimates for 1-6 class linear growth models for hyperactivity/impulsivity

Class	Class prevalence	Intercept Mean	Slope Mean	Intercept-slope covariance
		1-class model		
Class 1	1	-0.05	-0.33*	-0.34*
		2-class model		
Class 1	0.14	0.49*	.76*	-0.44*
Class 2	0.86	-0.14*	-.51*	-0.44*
		3-class model		
Class 1	.22	0.44*	-0.17*	0.47*
Class 2	.08	0.66*	1.03*	0.47*
Class 3	.71	-0.29*	-0.54*	0.47*
		4-class model		
Class 1	.08	1.10*	0.23	-0.07
Class 2	.13	1.33*	-1.69*	-0.07
Class 3	.73	-0.41*	-0.29*	-0.07
Class 4	.05	-0.53*	1.74*	-0.07
		5-class model		
Class 1	.07	-0.43*	1.43*	-0.10*
Class 2	.04	1.13*	0.72	-0.10*
Class 3	.08	1.29*	-2.06*	-0.10*
Class 4	.70	-0.43*	-0.32*	-0.10*
Class 5	.11	1.16*	-0.81*	-0.10*
		6-class model		
Class 1	.05	-0.35	1.71*	-0.15*
Class 2	.04	1.27*	0.60*	-0.15*
Class 3	.08	1.24*	-1.94*	-0.15*
Class 4	.58	-0.47*	-0.41*	-0.15*
Class 5	.17	-0.18*	0.23*	-0.15*
Class 6	.08	1.34*	-0.89*	-0.15*

Note. *statistically significant (p<.05).

Table 6: Parameter Estimates for 1-6 class linear+quadratic growth models for attention deficit

Class	Class prevalence	Intercept Mean	Linear Slope Mean	Quadratic Slope Mean	Intercept-Linear Slope Covariance	Intercept-Quadratic Slope Covariance	Linear Slope-Quadratic Slope Covariance
				1-class model			
Class 1	1	-0.04	-0.30*	0.24*	-0.60*	0.22	-1.76*
				2-class model			
Class 1	.70	-0.44*	-0.30	0.35*	-0.61*	0.33*	-1.76*
Class 2	.30	0.90*	-0.29	-0.03	-0.61*	0.33*	-1.76*
				3-class model			
Class 1	.14	1.48*	-1.56*	0.71	-0.22	0.10	-1.79*
Class 2	.51	-0.71*	0.18	0.04	-0.22	0.10	-1.79*
Class 3	.35	0.32*	-0.46*	0.33*	-0.22	0.10	-1.79*
				4-class model			
Class 1	.61	-0.45*	-0.19	0.09	-0.53*	0.33	-1.70*
Class 2	.10	1.51*	-0.84	-0.56	-0.53*	0.33	-1.70*
Class 3	.20	0.80*	-0.15	0.30	-0.53*	0.33	-1.70*
Class 4	.08	-0.47*	-0.71	2.15*	-0.53*	0.33	-1.70*

Note. *statistically significant (p<.05).

Table 7: Parameter Estimates for 1-6 class linear+quadratic growth models for hyperactivity/impulsivity

Class	Class prevalence	Intercept Mean	Linear Slope Mean	Quadratic Slope Mean	Intercept-Linear Slope Covariance	Intercept-Quadratic Slope Covariance	Lin Qu Slo Co
				1-class model			
Class 1	1	-0.03	-0.52*	0.19*	-0.40*	-0.07	-1.
				2-class model			
Class 1	.83	-0.11*	-0.38*	-0.19*	-0.33	-0.09	-1.
Class 2	.16	0.40*	-1.27*	2.12*	-0.33	-0.09	-1.
				3-class model			
Class 1	.10	0.22*	-3.05*	4.02*	-0.48*	0.07	-0.
Class 2	.09	0.80*	1.57*	-1.28*	-0.48*	0.07	-0.
Class 3	.81	-0.16*	-0.46*	-0.10	-0.48*	0.07	-0.

Note. *statistically significant (p<.05).